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Post-Irradiation Leiomyosarcoma of The Maxilla: Report of A Case in A Patient with Prior Radiation Treatment for Retinoblastoma

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Abstract

Post-irradiation sarcoma is a well-defined complication of radiation therapy, yet few reports document such lesions in the head and neck. A 30-year-old man presented for evaluation of an expansile lesion of the left posterior maxilla. His medical history was significant for a childhood ocular malignancy - unilateral retinoblastoma - which was treated with a combination of surgical enucleation of the eye and external beam radiation therapy. Biopsy of his maxillary lesion revealed a spindle cell malignancy that was morphologically and immunohistochemically consistent with a diagnosis of leiomyosarcoma. Further investigation into the case revealed that the patient had three children, every one of whom developed unilateral retinoblastoma in infancy. Compared to the more frequent presentation of bilateral tumors in hereditary cases of retinoblastoma, such cases of heritable unilateral retinoblastoma are exceptional. Importantly, heritable forms of retinoblastoma confer a significant risk for development of second primary cancers, necessitating long-term clinical follow-up in these patients.

1. Introduction

Post-irradiation sarcoma is a well-documented, though relatively uncommon, complication of radiation therapy.[1., 2., 3.] These tumors typically develop more than 10-15 years after radiation therapy for the primary malignancy.[4] While many types of malignancy have been reported in this setting, osteosarcoma, fibrosarcoma and malignant fibrous histiocytoma generally predominate in most series.[5., 6., 7., 8., 9.] Less commonly, subsequent development of leiomyosarcoma has been reported.[10., 11., 12.]

Leiomyosarcomas are malignant mesenchymal neoplasms of smooth muscle differentiation that account for 5-10% of all soft tissue sarcomas. These tumors are often divided into three anatomic groups: soft tissue, cutaneous, and vascular.[3] The most common sites where they develop are the gastrointestinal tract, the urinary tract and the female genital tract. Primary intraosseous leiomyosarcoma has also been documented.[13] Leiomyosarcomas occurring in the head and neck region, including the oral cavity, are uncommon.[14] In this report, we describe the development of leiomyosarcoma of the maxilla that was identified 28 years after the patient was treated with radiation therapy for unilateral retinoblastoma. Finally, we review the role of the retinoblastoma gene (RB1) in the pathogenesis of retinoblastoma, and discuss current concepts regarding post-irradiation sarcoma and second primary cancers in familial retinoblastoma.

2. Case report

A 30-year-old Amish man presented with the chief complaint of pain and expansion of his left upper jaw. The patient stated that a dental extraction had been performed three months earlier in an attempt to relieve the pain, but this had no impact on his symptoms. His medical history was significant for unilateral retinoblastoma, diagnosed at two years of age, and treated with exenteration of his left eye in addition to external beam radiation therapy. The patient did not know if there was any family history of this condition. Clinical examination revealed absence of the left eye and marked

atrophy of the orbital and superior maxillary regions bilaterally. Intraorally, a diffuse unilateral enlargement involving the left posterior maxilla was noted (Fig 1). The area was firm on palpation and showed no evidence of ulceration or color change. A periapical radiograph showed a homogenous loss of trabecular architecture in the form of ill-defined radiolucent change in the left posterior maxilla. Existing maxillary teeth in the area showed aberrant or abbreviated root development and loss of lamina dura (Fig 2).

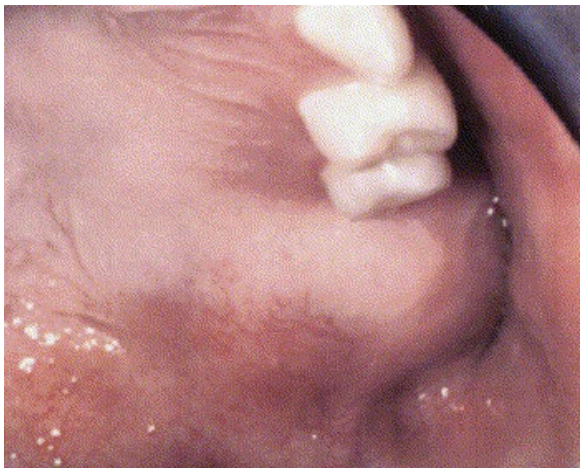

Fig 1. Clinical photograph showing a firm and non-ulcerated enlargement of the left posterior maxilla.

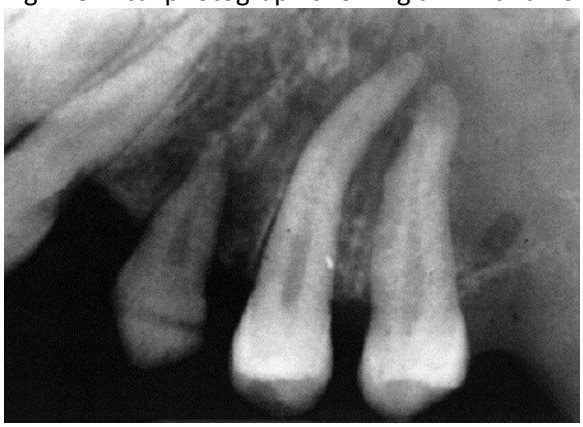

Fig 2. Periapical radiograph of the left posterior maxilla showing ill-defined radiolucent changes in the bone, widening of the periodontal ligament and loss of lamina dura.

Computerized tomography scans of the area, with and without contrast enhancement, confirmed the prior exenteration of the left eye in addition to demonstrating the maxillary tumor. Coronal, axial and sagittal sections revealed a maxillary tumor with its epicenter in the region of the left maxillary sinus. The tumor destroyed the lateral wall of the maxillary sinus and extended to the ipsilateral infratemporal fossa. It could not be determined unequivocally whether the epicenter was intraosseous or extraosseous. The lesion measured approximately 4.6 cm antero-posteriorly, 3.2 cm in its widest lateral dimension, and protruded posteriorly 2.5 cm into the left infratemporal fossa. The inferior portion of the mass involved the left maxillary alveolar ridge, while the superior portion of the lesion extended into the inferior orbital fissure, producing deformation of the fat planes.

An incisional biopsy of the intraoral mass was performed under local anesthesia. Histopathologic examination of hematoxylin and eosin-stained sections of the biopsy sample showed an infiltrating

cellular neoplasm composed of relatively uniform interlacing fascicles of spindle-shaped lesional cells (Fig 3). Lesional cells exhibited eosinophilic condensation of the cytoplasm, intranuclear and perinuclear vesiculation, and rare abnormal mitotic figures with no evidence of necrosis (Fig 4). The preliminary diagnosis of a spindle cell malignancy was made, and a panel of antibodies was applied to additional sections of the tissue using routine immunohistochemical techniques with high temperature antigen retrieval. Antibodies directed against cytokeratins (Novocastra, clone AE1/3), α-smooth muscle actin (Novocastra, clone asm-1), muscle specific actin (Novocastra, clone HHF35), vimentin (Novocastra, clone V9) and S-100 protein (Novocastra, clone S1/61/69) were used. These immunohistochemical studies indicated that the tumor cells were strongly reactive with antibodies directed against α-smooth muscle actin (Fig 5) and vimentin, modestly positive for muscle specific actin, and non-reactive for antibodies directed against cytokeratins and S-100 protein.

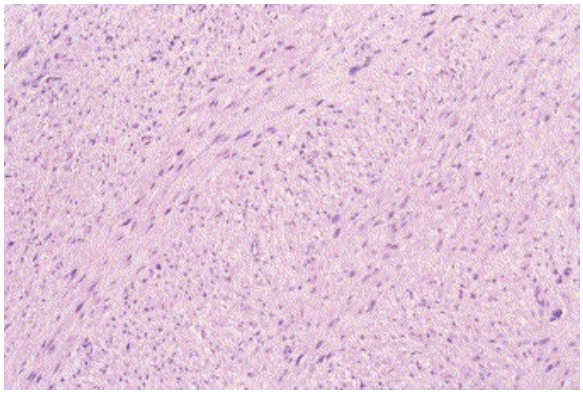

Fig 3. Low-power photomicrograph of the biopsy specimen showing a spindle cell neoplasm with an interlacing fascicular arrangement suggestive of leiomyosarcoma. (hematoxylin & eosin, original magnification × 200)

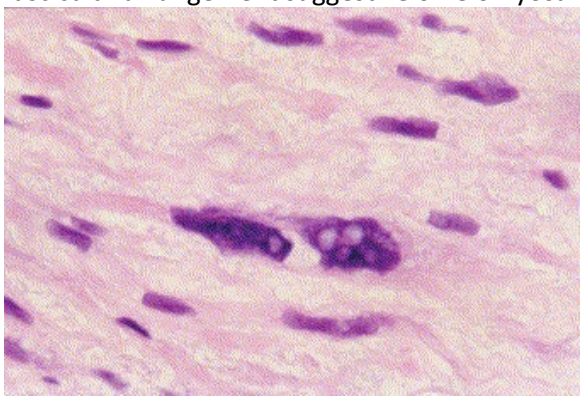

Fig 4. High-power photomicrograph demonstrating malignant cells with eosinophilic cytoplasm, hyperchromatic nuclei, and intranuclear and perinuclear vacuoles. (hematoxylin & eosin, original magnification × 600)

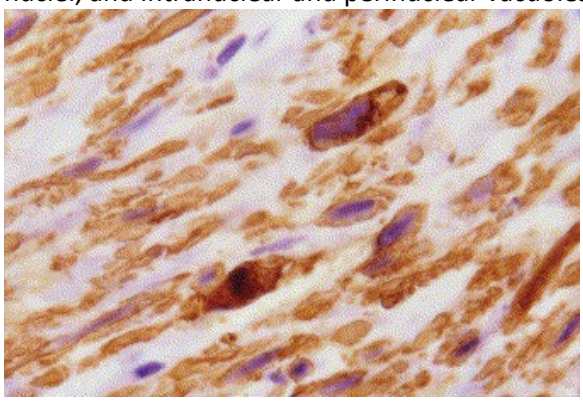

Fig 5. Lesional cells show diffuse strong cytoplasmic immunoreactivity for α-smooth muscle actin. (Harris hematoxylin, with immunohistochemical marker α-smooth muscle actin, original magnification × 600)

Based on immunohistochemical and histopathologic findings, a diagnosis of leiomyosarcoma was rendered. Subsequent imaging studies of the lungs and brain showed no evidence of metastatic disease. Surgical treatment consisted of a hemi-maxillectomy procedure that was performed under general anesthesia. A denture was fabricated to obturate the surgical defect, and the patient exhibited adequate speech and swallowing functions with the prosthesis in place. The histopathologic findings in the resected specimen were very similar to the original incisional biopsy specimen, with no evidence of necrosis, the rare presence of mitotic figures (<1 figure/10 high power field [HPF]; 0.174 mm^2/HPF), and a relatively well-differentiated spindle cell malignancy that was morphologically and immunohistochemically consistent with the previous diagnosis of leiomyosarcoma. The tumor was classified as Grade I using the FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer) or the NCI (National Cancer Institute) grading system.[15., 16., 17.] By means of the AJCC (American Joint Committee on Cancer) soft tissue sarcoma staging system, the tumor was assigned as T1 (tumor size<5cm), N0 (no nodal involvement), and M0 (no metastasis), classifying it as a Stage I grouping.[18]

During a follow-up appointment three years after treatment there was no indication of tumor recurrence. Further questioning revealed that since the patient was last seen, he and his wife had three children - twins and one other child. It was also discovered that all three children developed unilateral eye tumors that were treated surgically at the neighboring Children's Hospital. Each of these tumors proved to be retinoblastoma. Microscopic review of the histologic sections of each child's resected eye revealed a round blue cell tumor that completely filled the corpus vitreous of the involved eye (Fig 6). Flexner-Wintersteiner rosettes, a characteristic histologic feature in some cases of retinoblastoma, were identified in two of the tumors (Fig 7).

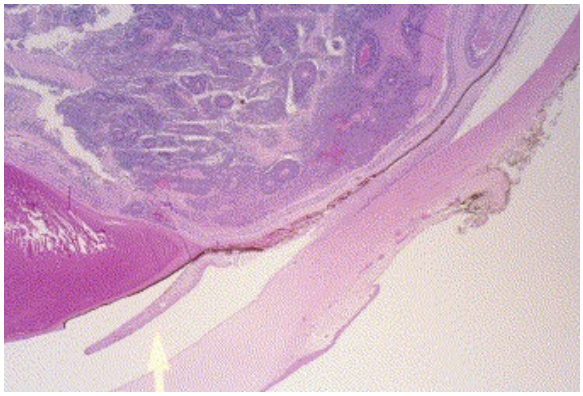

Fig 6. Low-power photomicrograph of the resected eye from one of the children in this case. Note the round blue cell tumor (retinoblastoma) filling the corpus vitreous of the eye. The arrow points to the iris of the eye for specimen orientation. (hematoxylin & eosin, original magnification × 100)

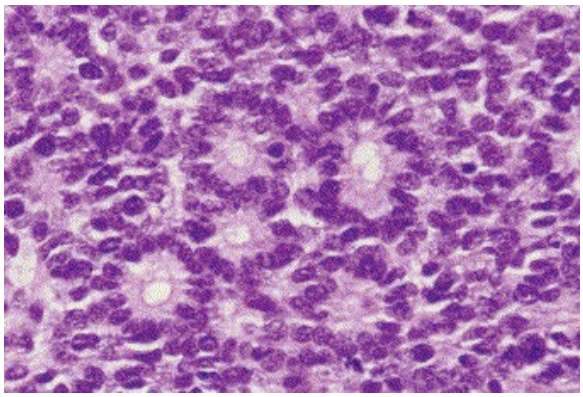

Fig 7. High-power photomicrograph of the tumor in figure 6 showing Flexner-Wintersteiner rosettes, characterized by circular clusters of cuboidal cells palisading around a central clear lumen outlined by eosinophilic apical cell membranes. (hematoxylin and eosin, original magnification × 600)

3. Discussion

Post-irradiation sarcoma represents an uncommon complication of radiation therapy, and a relatively small proportion of tumors arising in this setting can actually be designated as leiomyosarcoma. There are several criteria for the diagnosis of post-irradiation sarcoma: a previous history of radiotherapy to the area where the sarcoma arose; a long period of latency between radiation and the appearance of the tumor; and the histopathologic diagnosis of sarcoma.[3] The latency period between radiotherapy and the diagnosis of leiomyosarcoma has varied between 12-50 years in reported cases.[19., 20., 21., 22., 23.] For cases described prior to 1980 (before the widespread use of immunohistochemistry), the diagnosis was based mainly on histopathologic, or less commonly, ultrastructural features. More recently, immunohistochemical techniques have allowed for more accurate characterization of this sarcoma, although limitations exist. In our case, for example, immunoreactivity for smooth muscle actin does not permit an unequivocal diagnosis of a smooth muscle tumor such as leiomyosarcoma. Most actin antibodies commercially available are pan-actin moieties that cluster around 45 kd, so they are not muscle epitope-specific enough to demonstrate “pure” myogenous differentiation.[24] Therefore, these antibodies can react with many other cell types beside muscle, as seen by actin positivity in reactive lesions and in non-smooth muscle tumors such as synovial sarcoma, malignant fibrous histiocytoma, fibromatosis and nodular fasciitis.[25., 26., 27., 28.] This is a common problem in the immunohistochemical detection of heteropolymeric proteins like actin. Therefore, we acknowledge that immunoreactivity for actin in this case does not provide definitive evidence of smooth muscle differentiation, but combined with histopathologic features, leiomyosarcoma is arguably the most appropriate diagnosis.

The fact that this patient and all three of his children were affected with unilateral retinoblastoma, or a hereditary form of retinoblastoma, is significant to this case. Retinoblastoma is a rare malignant tumor of the retinal anlage that typically affects infants. The condition can be inherited or it can be acquired sporadically. Retinoblastoma arises when mutations induce a loss of function affecting both alleles at the retinoblastoma (RB1) gene locus on chromosome 13q.[29., 30.] Analysis of retinoblastoma tumor DNA indicates that the mutation is autosomal recessive and that tumors develop only when the function of both alleles is destroyed, illustrating Knudson's two-hit hypothesis. The mutant RB1 trait shows high penetrance and variable expressivity. Most individuals with germline RB1 mutations develop bilateral

retinoblastomas because mutations arise in several retinal cells in both eyes. In some exceptional families, as in this case, unilateral retinoblastoma is prevalent and has been referred to as low-penetrance retinoblastoma.[31] The RB1 gene product (P110) is an important tumor suppressor gene and cell cycle regulator. The protein is unphosphorylated in the G0 and G1 phase of the cell cycle and phosphorylated during the S and G2 phase. In its unphosphorylated state, the protein functions as a cell cycle suppressor.[32., 33.] In its absence, the cell proceeds to the next division without regulation, a critical step in the process of neoplastic transformation.

In retinoblastoma patients, the impact of radiation therapy in inducing second primary tumors has become more evident over the past few decades.[34., 35.] Originally, it was thought ionizing radiation-induced RB1 mutation was the sole cause of second primary tumors. However, studies suggest that ionizing radiation is not the cause of second primary cancers, but rather poses an increased risk for site-specific (field of radiation) carcinogenesis in this genetically susceptible population.[36] A dose-dependent carcinogenic effect has been demonstrated for most radiation-induced sarcomas.[37] In our case, however, records of radiation treatment details such as size of field and dosing could not be obtained from 30 years ago, so the possibility exists that the sarcoma in this case was not radiation-induced and arose outside the field of radiation, or would have eventually occurred even in the absence of radiation exposure. Retinoblastoma patients are considered genetically susceptible for the development of second primary tumors because all of their somatic cells have inherited an aberrant RB1 gene. Accordingly, recent evidence supports the idea that intrinsic factors, such as inherited genomic instability at the retinoblastoma locus, confer a significant risk for the development of second primary tumors in this population.[36] This is supported by the finding of nearly equal numbers of second primary cancers occurring inside and outside the radiation field in larger series.[38] Therefore, genetic predisposition has a substantial impact on risk of subsequent cancers in retinoblastoma patients, which may be further increased by radiation treatment through yet undetermined mechanisms.[37] On the contrary, some investigators contend that the relationship between radiation and second primary cancers may be coincidental. Additional molecular and genetic research, and further accrual and reporting of cases with long-term follow-up, may provide an improved understanding of the relationship between retinoblastoma, radiation therapy and second primary cancers in this population.

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